A METHOD OF MEASURING THE CRITICAL CLOSING PRESSURE OF DIGITAL VESSELS IN TOXEMIA OF PREGNANCY

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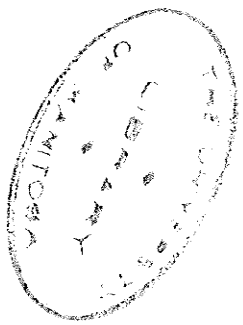

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ABSTRACT

I A review of the literature on toxemia of pregnancy reveals the fact that there have been many hypotheses aimed at explaining the elevation of blood pressure that is characteristic of the disease. The exponents of the various hypotheses seem to agree that the toxemic hypertension is due to an increase in peripheral vascular resistance.

II A method has been developed for measuring digital critical closing pressure (ccp) as defined by Burton. In accordance with Burton's suggestion, the transmural pressure of the digital vessels was lowered by artificially increasing the extravascular pressure. The lowest transmural pressure at which blood flow was evident, by direct observation of the eponychial capillaries was determined and taken to represent the c.c.p.

From a study of the influence of various factors (body heating and cooling, local ischemia, conduction anesthesia, venous pressure etc) upon the c.c.p., it was concluded that c.c.p. is a property of the vessel wall.

The method of c.c.p. measurement was applied to normal and hypertensive subjects. The finding that c.c.p. is higher in the hypertensive subjects supports the view that hypertension is the result of changes in the state of the vessel walls.

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PART I TOXEMIA OF PREGNANCY

A INTRODUCTION

Dieckmann (19) defines toxemia of pregnancy as a condition occurring during pregnancy or the early puerperium which is characterized by one or more of the following abnormalities: edema, proteinuria, hypertension, convulsions and coma. The diagnosis of preeclampsia-eclampsia (the two toxemia of pregnancy) is made when toxemic signs appear in a pregnant woman and there is no history or other convincing evidence to suggest that such diseases as essential hypertension, kidney disease, or epilepsy are responsible for these signs. The following account will deal where possible with only preeclampsia-eclampsia. Because it is the hypertension in toxemia with which we are concerned primarily, attention will be focussed upon that aspect of the disease.

B THE MECHANISM OF THE HYPERTENSION OF TOXEMIA

The factors which could be involved in the production and maintenance of any hypertensive state are: (i)increased cardiac output, (ii)increased blood volume, (iii)increased blood viscosity, and (iv)increased peripheral resistance.

Wenkebach (90a) found that the cardiac output in toxemic patients was the same as that in normal pregnant patients, and that the blood volume in toxemic patients was lower than that of normal pregnant patients. Dieckmann (21) reported that the blood viscosity in preeclampsia-eclampsia was higher than that in normal pregnancy only in severe cases (with hemoconcentration). He concluded that the hypertension of toxemia must be due to an elevated peripheral resistance, resulting most probably from an increased vascular tone in the arterioles.

Many investigators have supported the contention that vasospasm is the basis of the elevated blood pressure found in toxemia.

In 1920 Hinselmann (46), in viewing the nail bed microscopically, described narrowing of the capillary loops in toxemia. He attributed this to arteriolar spasm. In 1939 Hyline (67), on funduscopic examination, noticed retinal arteriolar spasm in toxemic patients. McCall (64) studied cerebral hemodynamics by the nitrous oxide method, and concluded that in toxemia the cerebrovascular resistance was elevated due to vasospasm. Turner and Houck (96) and Dieckmann (23) believe that the decreased renal blood flow (diodrast clearance) and glomerular filtration rate (inulin clearance) that they found in toxemia are the result of arteriolar constriction. McCall (65) claims that several investigators have demonstrated that in toxemia there is an increased hepatic vascular resistance, which he feels is due to increased vascular tone.

C THE PRESSOR AND DEPRESSOR RESPONSES IN TOXEMIA

In considering the nature of the elevated blood pressure of toxemia, it is of interest to note how that blood pressure responds to various pressor and depressor stimuli.

Page (74) states that in toxemia there is an increased response to the cold pressor test. Dieckmann (26) feels that this test has much prognostic significance, that in women whose systolic pressure undergoes a rise of more than 30 mm Hg he recommends no future pregnancies. The Cheneys (9), on the other hand, in testing 500 pregnant patients, found no correlation between existing or impending toxemia and hyperactive responses to cold. Page (74), Dieckmann and Michel (28), and deValera and Keller (25) have all found that the pressor response to injected pituitrin is greater in toxemia than it is in normal pregnancy or essential hypertension of pregnancy.

Gerber et al (34) were unable to cause a significant blood pressure drop in toxemic patients by the administration of a ganglionic blocking

agent (2240) or a high spinal anaesthetic. The depressor response to such treatment was considerably greater in cases of essential hypertension of pregnancy. Kistner (53) and others have reported that the depressor response to aprosoline or veratrum viride is far more profound in toxemia than it is in normal pregnancy or essential hypertension of pregnancy.

D THE CAUSE OF THE HYPERTENSION OF TOXEMIA

The exact nature of the pressor mechanism involved in toxemia has been the subject of much controversy. Several theories have been put forward, most of which implicate humoral action. None has been accepted unanimously. A consideration of the more strongly supported theories shall follow:

1. Renin and Angiotonin:

Most investigators (4, 14, 33, 58, 96) have found the renal blood flow to be significantly lower in toxemic pregnancy than in normal pregnancy. If we accept this finding, we must consider the possibility that renal ischemia is the physiological abnormality underlying the toxemic state.

Ever since 1934, when Goldblatt and his associates (36) produced hypertension in experimental animals by carefully regulated constriction of the renal arteries, a relationship between the blood flow to the kidneys and systemic blood pressure has been recognized. Other investigators have caused hypertension in animals by interfering in various ways with the renal circulation. Page (76) wrapped the animals' kidneys in silk or cellophane, and the resultant scarring caused a compression ischemia of the organs; Moses(66) occluded small renal vessels with finely divided silica which he injected into the renal artery. It was shown by Page (76) and Freeman (30) that neither denervation of the kidneys nor extensive sympathectomy protected the animals against this so called "renal hypertension." They concluded that the pressor effect must be due to the

release of some humoral substance by the ischemic kidney. As early as 1898 Tigerstedt and Bergman (93) had reported that saline extracts of normal rabbit kidneys, when injected into other normal rabbits, caused an elevation of blood pressure. They felt that this was due to a pressor substance in the normal kidney which they called "renin." In 1940 Page and Helmer (77) introduced the hypothesis that the ischemic kidney releases an enzyme "renin" which converts "renin substrate", a substance present in the globulin fraction of the serum proteins into "angiotonin", which acts directly upon the blood vessel walls causing vasoconstriction, increased peripheral resistance, and hypertension. This hypothesis has enjoyed considerable popularity ever since its original publication.

Several attempts have been made to show that interference with the renal blood supply of pregnant animals will cause a toxemic picture to develop. Dill and Erickson (27) found that partial constriction of the renal arteries of pregnant dogs brought about, within two to five days, hypertension, hematuria, albuminuria, nitrogen retention, lassitude, convulsions, coma, and death. Non-pregnant control dogs developed no such picture in the same period of time. Furthermore, termination of pregnancy led to rapid improvement of the affected animals. I. Page (86) found that similar signs and symptoms appeared when he clamped the renal arteries of pregnant dogs, but in his series delivery failed to bring about a reduction in blood pressure. M. Page and Ogden (86) reported that renal arterial constriction in pregnant rabbits failed to cause any hypertension until after delivery. Since the experimental procedures of the above three groups were essentially the same it is difficult to explain the disagreement of their results. Of the three studies, only that of Dill and Erickson supports the possibility that toxemia is due to renal ischemia in an animal rendered susceptible by pregnancy to the resulting pressor mechanism.

One explanation of why the renal blood flow is decreased in toxemia has been offered by Sophian (97). Franklin and Winstone (29) reported that stretching the uterus of rabbits caused renal cortical ischemia (RCI). Sophian believes that the hypertension of toxemia is the result of a utero-renal reflex, whereby myometrial resistance to distention causes RCI. He feels that this hypothesis explains the high incidence of toxemia in primigravity and hydramnios. Reynolds and Baker (80) reported that the primigravid uterus has increased resistance to stretch. Smythe (86) was able to alleviate the clinical picture of toxemia by manfotic tap. Sophian suggests that the utero-renal reflex is mediated by the uterine and lesser splanchnic nerves. Theobald (92) found that denervation of the uterus had a marked prophylactic effect against toxemia. Dexter and Haynes (17) found renin in toxemic blood. They suggested that the renin might be of placental rather than renal origin. Page and Glenkeating (75), however, found that extracts of toxemic placentae did not cause convulsions in DOA-NaCl hypertensive rats (see section on corticosteroids) while renin did.

3. The Corticosteroids:

Ever since 1937, when Goldblatt (37) concluded that the adrenal gland was essential to the production and maintenance of experimental renal hypertension, a great deal of attention has been paid to the possible relationship between the blood pressure and the secretion of cortico-steroids. It is felt generally that this group of hormones influences also the excretion of water and electrolytes. Since hypertension and water and electrolyte retention are the cardinal features of toxemia, much interest has been directed toward the role of the corticosteroids in the pathogenesis of this disorder.

In 1946 Venning (97) reported that the urinary corticoids in

normal pregnant women showed two transient increases above the normal non-pregnant levels, the first during the first trimester and the second during the third trimester. She found that in toxemic pregnancies these rises were both sustained and exaggerated. In 1954 Venning and her associates (90) went on to show that the glucocorticoids were depressed in toxemia and that the increase in total corticoids was due largely to the Rs-retaining or DOA-like steroids. Hughes et al (49) reported that the rises in urinary corticoids in both normal and toxemic pregnancy are due invariably to increases in the yeasty-water-soluble fraction, which by paper chromatography resembles DOA. Other investigators also (8, 88, 94) have been able to corroborate the findings of Venning and her group.

While most observers have assumed that adrenocortical hypersecretion accounts for the increase in DOA-like steroids found in toxemic urine, a few have favored the suggestion that the hormones are liberated by the toxemic placenta. Gordon et al (30), however, reported that extracts of toxemic placentas do not contain appreciable DOA-like steroids. Nestbeom (63) believes that the normal placenta converts mineralocorticoids into progesterone. To feels that the failure of the toxemic placenta to do this accounts for the increased corticoids and decreased progesterone that be found in toxemic urine. An adequately proven explanation for the increased urinary DOA-like steroids of toxemia, however, is lacking.

If we can accept as valid the finding that the DOA-like corticoids are elevated in toxemia, we must consider the possibility that these hormones, when in excess, are related etiologically to the disease. In doing so it seems necessary to review some of the work of those investigators who studied the effects of administering excess DOA to humans and experimental animals. Loeb and his associates (57, 79) were able to induce hypertension in both normal and Addisonian humans

by repeated injections of the steroid. Friedman et al (51, 52) reported a pressor response in rats to very small amounts of DOA. This response could be prolonged and exaggerated by uninephrectomy and force fed NaCl. Hasson et al (59, 60, 61) found that the pathological and clinical pictures produced in non-pregnant rats by the administration of DOA and NaCl closely resembled those of human preeclampsia. The animals rendered preeclamptic-like by this treatment convulsed when given renin or angiotonin. The same rats did not convulse when given pituitrin, epinephrine, or nor-epinephrine, nor did normal untreated rats when given renin or angiotonin. Page and Bloedorn (75) having repeated the work of Hasson's group with similar results, believe that excess DOA and NaCl sensitize the arterioles to the renin-angiotonin mechanism (described earlier). They feel that certain pregnant women, with abnormally elevated DOA-like steroids, and unrestricted NaCl ingestion, are likewise sensitized and in this way become toxemic.

B. Posterior Pituitary Hormones:

Because the posterior pituitary gland is known to secrete hormones which have pressor and antidiuretic actions, many investigators have considered the possibility that toxemia of pregnancy may be due to hyperactivity of this gland. In 1931 Anselmino and Hoffman (1) found, in ultrafiltrates of toxemic blood, a substance functionally resembling posterior pituitary extract; but their experiments were not controlled and several others (16, 49, 61, 89) in examining toxemic blood have failed to demonstrate any significant increase in pressor or antidiuretic activity. Numerous investigators (12, 41, 84, 90) have reported that the antidiuretic activity of toxemic urine exceeds that of normal pregnant urine. Lloyd et al (56), however, have pointed out that this finding could be the result of bacterial contamination, this group having

shown that B.Coli will impart antidiuretic activity to urine specimens.

Evidence is lacking that any pressor or antidiuretic activity of toxemic blood or urine is due to posterior pituitary secretions. Sophian (86) has suggested that such activity may be due to the presence of renin from ischemic kidneys. Ken and Landis (42) believe that the placenta is the origin of the pressor and antidiuretic substances. They extracted such substances from all placentas examined, the highest concentrations coming from toxemic organs. Byron (7), however, found no difference between the antidiuretic titers of normal and toxemic placental extracts. Cheeley and Kolhaul (10) feels that the antidiuretic substance comes from an ischemic placenta. They base their view upon the results of perfusion experiments done on isolated hyperemic and ischemic human placental cotyledons.

Many investigators are reluctant to accept the very inconclusive finding of elevated posterior pituitary-like substances in toxemia, and feel that if pituitrin is responsible for the disease, it is because the toxemic patient is for some reason hypersensitive to the hormone, even in normally existing concentrations. Diedmann(24) and Page (71) both found that transfusions of toxemic blood, when given to normal pregnant women, had neither a pressor nor an antidiuretic effect. Page (74), Diedmann and Michel (13), and deValera and Keller (15) have all shown that toxemic patients have an exaggerated pressor response to injected pituitrin, when compared to normal pregnant controls.

No one has offered an acceptable explanation for the hypersensitivity to pituitrin in toxemia. In 1935 Keller and Urban (45) reported that extracts of liver, muscle, brain, or kidney had the power to inactivate posterior pituitary extracts in vitro. Whole blood also did this, but to a lesser extent. Fukata (28) discovered that the serum from normal pregnant women in the third trimester inactivated pitocin

in vitro, that from normal pregnant women in the first trimester had a very limited ability to do so. Woodbury et al (100) found that the oxytocic fraction of the posterior pituitary secretion was inactivated more rapidly when incubated with blood from women in the last four months of normal pregnancy than when incubated with blood from normal non-pregnant women. This work suggests that the normal pregnant woman, during the later months of her pregnancy, is equipped with a defence mechanism against posterior pituitary secretions. It is conceivable that such a defence mechanism is lacking in the toxemic woman. Unfortunately, however, it remains to be shown that toxemic blood or serum fails to neutralize pituitrin.

4. The Sex Hormones:

A few investigators feel that toxemia of pregnancy is related in some way to abnormalities in the secretion of estrogens, progesterone, and gonadotrophic hormones (GTH). The Smiths (95) claim that a decreased urinary excretion of estrogens and pregnanediol and an increased urinary excretion of GTH (as compared to normal pregnant levels) preceded any clinical manifestation of the disease in almost all of their toxemic patients. Hughes et al (49) and Inge (74) have found that similar abnormalities in these urinary hormone levels existed in patients with clinically diagnosed toxemia.

After the first trimester of pregnancy estrogens and progesterone are secreted chiefly by the syncytial cells of the chorionic villi, and GTH by the Langhans cells. The Smiths have noted deterioration of both types of cell in the toxemic placenta but have made no attempt to account for this. While deterioration of the syncytial cells might be responsible for the decreases in urinary estrogens and pregnanediol, the deterioration of Langhans cells and the elevated urinary GTH seem to be paradoxical findings. The Smiths have tried to explain this paradox by suggesting that the elevated urinary GTH is the result of decreased utilization

rather than increased excretion of the hormone. They present no convincing evidence, however, in support of this suggestion.

The Smiths (83) have reported that the administration of diethylstilbestrol to pregnant women will raise the urinary excretion of both estrogens and pregnanediol, lower that of 17KS, and decrease the incidence of toxemia. Somerville et al (85), however, found in a similar study that diethylstilbestrol failed to do any of these things.

The Smiths feel that when the estrogen and progesterone levels are insufficient, decidual tissue undergoes catabolic changes. Toxic proteins, similar to menstrual euglobulin, are formed during the breakdown process and are absorbed into the circulation. These toxins are thought by the Smiths to cause vasospasm. This would lead to the completion of a vicious circle by limiting the blood supply to the placenta and thereby causing further syncytial deterioration.

This highly speculative hypothesis has received little in the way of outside support. Abnormal urinary sex hormone levels (the one corroborated finding upon which the Smiths have apparently based their views) could be the result rather than the cause of toxemia, and neither the Smiths nor any other investigators have presented acceptable evidence to the contrary.

5. Placental and/or Decidual Substances:

Currently the most popular theory is that preeclampsia-eclampsia is caused by some toxic substance liberated into the blood stream by the pregnant uterus or its contents.

Several investigators feel that this liberation is initiated by uterine ischemia. It has long been recognized that the incidence of toxemia is increased by multiple pregnancy and hydramnios, both of which could interfere with the uterine blood supply. Page (72) has pointed out that toxemia usually occurs late in pregnancy, when fetal demands for an increased blood supply could cause a relative uterine

ischemia. He has pointed out also that when the disease occurs early in pregnancy, it is usually associated with a hydatidiform mole, which he feels requires a blood supply greater than that to the normal uterine contents. In acute experiments, Ogden et al (70) and Hasthoon (62 caused a rapid elevation of the blood pressure in pregnant dogs by restricting the flow through the uterine arteries. Non-pregnant control dogs, treated similarly, showed no such pressor response. Dieckmann (74), however, noted that during hysterectomies on pregnant humans, the blood pressure did not rise significantly when the uterine arteries were clamped, but he does not state whether or not unclamped veins were available for taking from the uterus to reach the general circulation. Browne et al (5), using radioactive sodium measurements, demonstrated that the uterine blood flow in preeclampsia was significantly lower than that in normal pregnancy. He found a similar decrease in cases of essential hypertension of pregnancy, however, and feels that the uterine ischemia is the result and not the cause of the hypertension. Chesley and Alter (11) have reported that perfusates of ischemic human placental cotyledons, when injected into non-pregnant rabbits, caused several of the clinical and pathological features of toxemia to appear. When the cotyledons were not ischemic, similar changes were noted less frequently.

An association between placental degeneration and toxemia of pregnancy has been pointed out by several observers. Zeek and Assali (103 report that the vessels in over 75% of toxemic placentas show acute atheromatous changes, while in non-toxemic placentas vascular pathology is rare. Kenney and Hafner (91) noted an increased degree of degeneration of the syncytial cells in toxemia, leading to 70-90% "naked villi". Bartholomew (23) found a close relationship between placental degeneratio or infarction and toxemia. He feels, however, that very gross infarction will produce abruptio placentae rather than toxemia. Hunt et al (50)

believe that the degenerated placental tissue liberates autolysates, which in sufficient quantity will produce toxemia. Hunter (43) agrees that placental lesions are found more frequently in toxemia than in normal pregnancy, but suggests that these lesions are the result rather than the cause of the disease. Brant and Nadar (95), in studying 1500 placentae, concluded that there was no significant relationship between placental pathology and toxemia.

The nature of the toxic product which might be liberated by the placenta has been the subject of some controversy. The possible role of th placenta in the renin, corticosteroid, and posterior pituitary hormone theories has been considered earlier. Other toxic substances of which the placenta might be the source will be dealt with briefly.

(a) Epinephrine and Norepinephrine: It has been suggested that epinephrine or norepinephrine might be the placental toxin. Assali and Brotzman (2) feel that they have excluded this possibility. The hypertension resulting from these substances is reduced by benzodiazene and augmented by EDAC. They obtained neither effect in toxemic hypertension.

(b) Histamine: A few investigators feel that histamine is the toxin that causes preeclampsia-eclampsia. Hofbauer (47) by repeated small injections of histamine into non-pregnant cats produced eclampsia-like liver pathology. Abruptio placentae resulted when pregnant cats were treated similarly. Guillemin and Fortier (40) found that histamine aggravated the hypertension in DOA-NaCl rats, and that antihistamine alleviated it. Hoffman (46) reported good results in treating toxemic women with antihistamines but his study was not controlled properly. While it has been suggested that the placenta might be the source of histamine, good supporting evidence is lacking.

(c) Thromboplastin: Schneider (81) suggests that the pathology of

toxemia may be due to the release of thromboplastic substances from the placenta or decidua. He reports that human decidual extract injected into non-pregnant mice caused convulsive death, post mortem examination revealing intravascular thrombin plugs with haemorrhagic necrosis in the lungs, livers, and brains of the injected animals. A similar picture developed in pregnant rabbits when their placentae were traumatised. Page (74) and Diechmann (30) both found the human placenta and decidua to be very rich in thromboplastin. Diechmann (30) reports that fibrinogen is low or absent in the blood of some eclamptic patients, who develop a bleeding tendency. He feels that this is the result of placental thromboplastin causing intravascular clotting due to placental thromboplastin release could cause hypertension, either by a mechanically increasing the peripheral resistance, or by limiting the blood supply of an organ that will cause hypertension when ischemic (e.g. the kidney).

(d) Miscellaneous Toxic Proteins: The Smiths (29), as mentioned previously, feel that toxemia is caused by a toxic euglobulin produced in the breakdown of decidual tissue when the sex hormone levels are insufficient. Several other investigators have attributed the disease to the release of protein wastes from the catabolism of the decidua or placenta. None of their work, however, has been particularly convincing.

Obata (69) found that the saline extracts of both toxemic and normal human placentae, when injected intravenously into non-pregnant rabbits, caused the clinical picture and liver pathology of toxemia. If the placental extract was incubated with normal pregnant or non-pregnant human serum before injection, its toxic effect was minimized or abolished. Incubation with toxemic serum,

however, failed to neutralize the extract to any significant degree. Ohata concluded that toxemia occurs when the body is unable to neutralize a placental toxin which is present in all pregnancies. Hayashi (44) repeated the work of Ohata with similar results and conclusions. Sloan (26) reported that the normally occurring proteolytic ferments of the blood were increased during normal pregnancy. Ohata found the level of these enzymes to be very low in eclamptic blood. He suggests that the proteolytic enzymes may constitute the defence mechanism against toxic proteins liberated by all placentae, and that their absence may be the basis of toxemia.

6. Cerebrotonin:

An interesting pressor mechanism, which could conceivably play a part in the production of the hypertension of toxemia, has been described recently by Taylor and his associates (68, 69). They found that appropriate stimulation of the vagus or other peripheral nerves in non-pregnant dogs caused a hypertensive response. Since blood from the stimulated dog brought about a similar rise in blood pressure, when cross-circulated into an unstimulated dog, they concluded that the pressor mechanism must be due to the release, from the CNS, of a humoral substance, "cerebrotonin". The response could still be elicited when, by the administration of yohimbine and benzodiazane, the pressor effects of epinephrine and norepinephrine had been abolished. They felt therefore that cerebrotonin could not be epinephrine or norepinephrine. I suggest that in certain pregnancies abdominal distention provides the peripheral nerve stimulation necessary for the release of cerebrotonin, and that this humoral agent plays a role in the production of toxemia. Support for

this suggestion might be drawn from the fact that ayrocoline will both block the "serotonin mechanism" (80, 89) and alleviate the hypertension of toxemia (88) but will not abolish the pressor activity of pituitrin, norepinephrin and epinephrin, or renin.

E. CONCLUSION

The various mechanisms described are by no means completely incompatable. Indeed it seems probable that several factors act in conjunction with one another to produce preeclampsia-eclampsia, with its elevated blood pressure.

It is important to note that the exponents of all of the above theories agree that the hypertension of toxemia is due to an increase in peripheral vascular resistance. This is most probably the result of an increased vascular tone. The remainder of this presentation will deal with the investigation of a method for measuring this component of peripheral vascular resistance.

PART II CRITICAL CLOSING PRESSURE (C.C.P.)

A INTRODUCTION

1. The C.C.P. Concept:

Burton (6) has defined C.C.P. as that transmural pressure below which flow no longer occurs. Transmural pressure is defined as intravascular pressure minus extravascular pressure. The assumption has been made that a vessel is affected equally by any combination of intravascular and extravascular pressures that give the same transmural pressure.

Burton (5) feels that C.C.P. exists because the blood vessels have a tendency to close. He believes that this tendency is most profound in the arterioles, and suggests that these are the vessels responsible for C.C.P. as measured.

Burton (5) has proposed that the C.C.P. might serve as a more valuable index of peripheral vascular resistance than the commonly used pressure/flow ratio. The pressure/flow ratio is dependent upon the viscosity of the blood as well as the state of the vessels. The C.C.P. is dependent only upon the state of the vessels, the effect of viscosity being negligible since C.C.P. is measured at a time when blood flow is very limited or absent.

2. The Measurement of C.C.P. in Animals:

In 1951 Nichol et al (60), in perfusing the hind leg of a frog with Ringer's Solution, noted that the pressure of the perfusion fluid had to exceed a certain minimal level before flow occurred. They regarded this minimal pressure as the C.C.P., because under the conditions of their experiment the extravascular pressure (tissue pressure) was negligible and the transmural pressure was therefore equal to the intravascular pressure (perfusion pressure).

Other observers have made findings similar to those of Nichol et al

without attributing them to c.c.p. In 1953 Whittaker and Winton (99), in plotting the flow-pressure relationship of a dog's hind leg perfused with blood, found that their curves when extrapolated cut the pressure axis at a positive value. Similar positive pressure intercepts have been noted by Rappenheimer and Rhes (78), by Green et al (59), and by Levy and Shaw (68), all of whom perfused the hind legs of dogs with blood.

3. The Measurement of c.c.p. in Humans:

In measuring c.c.p. in animals, the transmural pressure was lowered (until transmural pressure equalled c.c.p. and flow ceased) by decreasing the intravascular pressure (perfusion pressure) while the extravascular pressure (tissue pressure) remained constantly negligible. In measuring c.c.p. in humans, the transmural pressure is lowered by increasing the extravascular pressure while the intravascular pressure (blood pressure) remains relatively constant.

Yamada (101), in determining the c.c.p. in the human finger, took the auscultatory brachial blood pressure of the contralateral arm as the intravascular pressure. He measured blood flow by means of a venous occlusion plethysmograph into which the extravascular pressure had been introduced. The extravascular pressure was increased by 5 mm Hg for each successive blood flow estimation. The lowest extravascular pressure at which flow no longer occurred was subtracted from the brachial blood pressure to give the c.c.p.

In our experiments, an attempt has been made to improve upon Yamada's method for measuring digital c.c.p.

B METHOD

1. Blood Flow Observation:

A small glass cover slip was placed over the nail bed of the experimental finger and fastened there with sticky wax. The space

between the cover slip and the nail bed was filled with glycerine. The finger was then enclosed in a transparent plastic plethysmograph. The airtight connection between the finger and the plethysmograph was made with thin rubber tubing and plastic adhesive tape. Care was taken to avoid interference with digital blood flow by the apparatus. Calcium chloride crystals were placed in the plethysmograph to absorb perspiration and prevent fogging of the visual pathway. The finger, thus prepared, was placed on the stage of a dissecting microscope, through which eponychial capillary blood flow could be observed. A mercury vapor lamp was used to illuminate the nail bed. (see figure 1.)

2. Measurement of Intravascular Pressure:

The digital systolic pressure of the experimental finger was taken as the intravascular pressure. The method for measuring digital blood pressure was as follows:

A stethoscope ear piece was connected to the finger plethysmograph by means of rubber tubing, and a pneumatic cuff was placed around the finger proximal to the plethysmograph. (see figure 2.) As the pressure in the pneumatic cuff was released gradually, from a level well above the systolic pressure, the cuff pressures at which a pulsing sound was first and last heard through the stethoscope were noted and taken to represent digital systolic and diastolic pressures, respectively.

The pneumatic cuff used in measuring the digital blood pressure had to be wide enough that the full cuff pressure was transmitted down to a sufficient length of the digital artery to cause its obstruction. The following experiment was aimed at determining the minimum width of cuff to be used:

Digital blood pressures were measured with five cuffs of different widths (3/8", 3/4", 1-1/8", 1-1/2", and 1-3/4"). Six digital blood pressure estimations were made with each cuff on each of five normal males, age 20-25 years. The cuffs were used in the following sequence: in the first

Figure 1. Apparatus for the Microscopic Observation of Dorsal Capillary Blood Flow

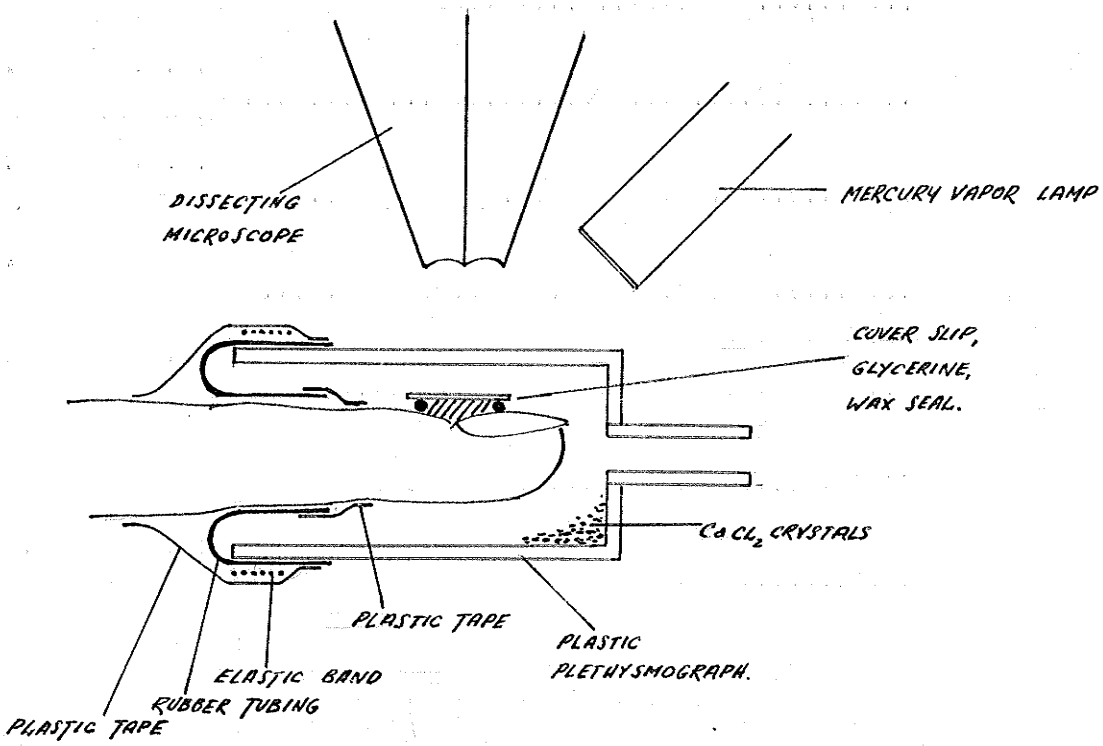
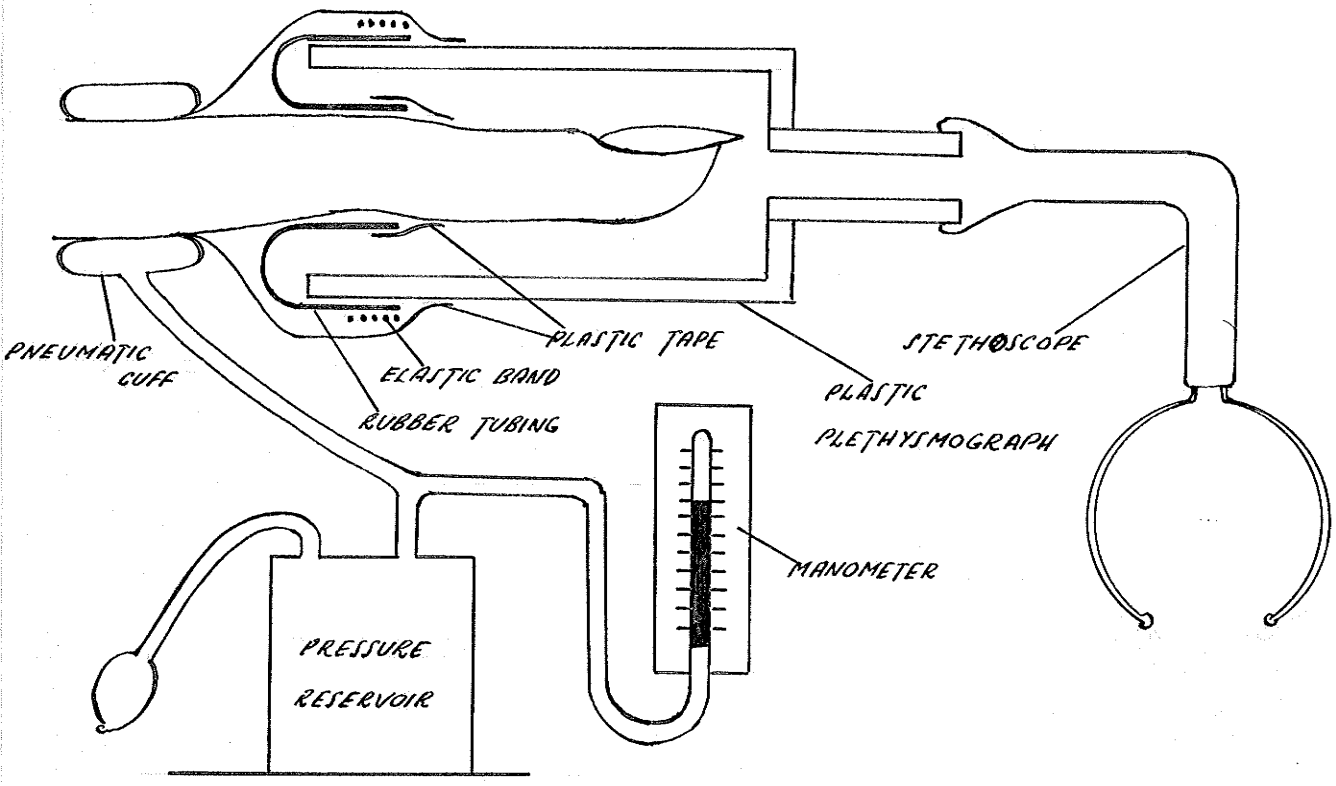


Figure 2. Apparatus for Measuring Digital Blood Pressure by the Auscultatory Method



subject 1,2,3,4,5,1,2,3,4,5,1,..... in the second subject 2,3,4,5,1,2,3,4,5,1,2,..... in the third subject 3,4,5,1,2,3,4,5,1,2,3,..... etc. The results have been tabulated in table 1 and charted in figure 3. Provided that the cuff width was 1-1/8" or more, the digital blood pressure did not vary appreciably with different cuff widths. Therefore in all experiments to follow, digital blood pressure was measured with a cuff 1-1/8" or wider.

Two other experiments were carried out, aimed at proving the validity of the digital systolic pressures attained by the auscultatory method. (Experiments to prove the validity of the auscultatory digital diastolic pressures will not be considered because the digital diastolic pressure does not enter into the calculation of the C.C.P.)

Experiment (a) The finger was prepared for microscopic observation of the eponychial capillaries. A pneumatic cuff was applied to the finger and inflated by a pressure well above systolic pressure. This caused cessation of flow in the eponychial capillaries. The cuff pressure was then released gradually and that pressure at which eponychial blood flow resumed was noted and taken to represent digital systolic pressure. Digital systolic pressure was then measured in the same finger by the auscultatory method. The procedure was repeated six times on each of six normal males, age 22-27 years. The digital systolic pressures attained by the two methods (visual and auscultatory) were statistically the same. (see table 2.)

Experiment (b) A plethysmograph was sealed onto the finger and connected by a Y-piece and rubber tubing to the ear piece of a stethoscope and to a tambour. The ear plugs of the stethoscope were dipped in heavy oil so that their connection to the ears was relatively airtight. A mirror was fastened onto the tambour to reflect a beam of light from a mercury vapor lamp onto a moving photosensitive paper. A pneumatic cuff was placed on the finger proximal to the plethysmograph

Table 1. Auscultatory Digital Blood Pressure as Measured by Pneumatic Finger Cuffs of Different Widths

Subject				Cuff Width and Digital Blood Pressure				
				3/8"	3/4"	1-1/8"	1-1/2"	1-3/4"
A.A.	23 yrs	normal	male	160/120	119/70	115/76	116/67	107/79
E.H.	25 yrs	"	"	167/98	153/65	122/66	124/64	120/64
G.G.	23 yrs	"	"	166/99	120/63	100/61	103/65	113/66
L.L.	20 yrs	"	"	151/114	116/77	112/68	109/69	105/63
S.L.	23 yrs	"	"	159/100	142/76	116/73	107/75	117/69
MEAN				162/106	126/72	114/69	113/68	112/68

Note: Each digital blood pressure listed represents the mean of six estimations on one subject.

Figure 3. Auscultatory Digital Blood Pressure as Measured with Pneumatic Finger Cuffs of Different Widths

(each point represents the mean of six estimations on one subject)

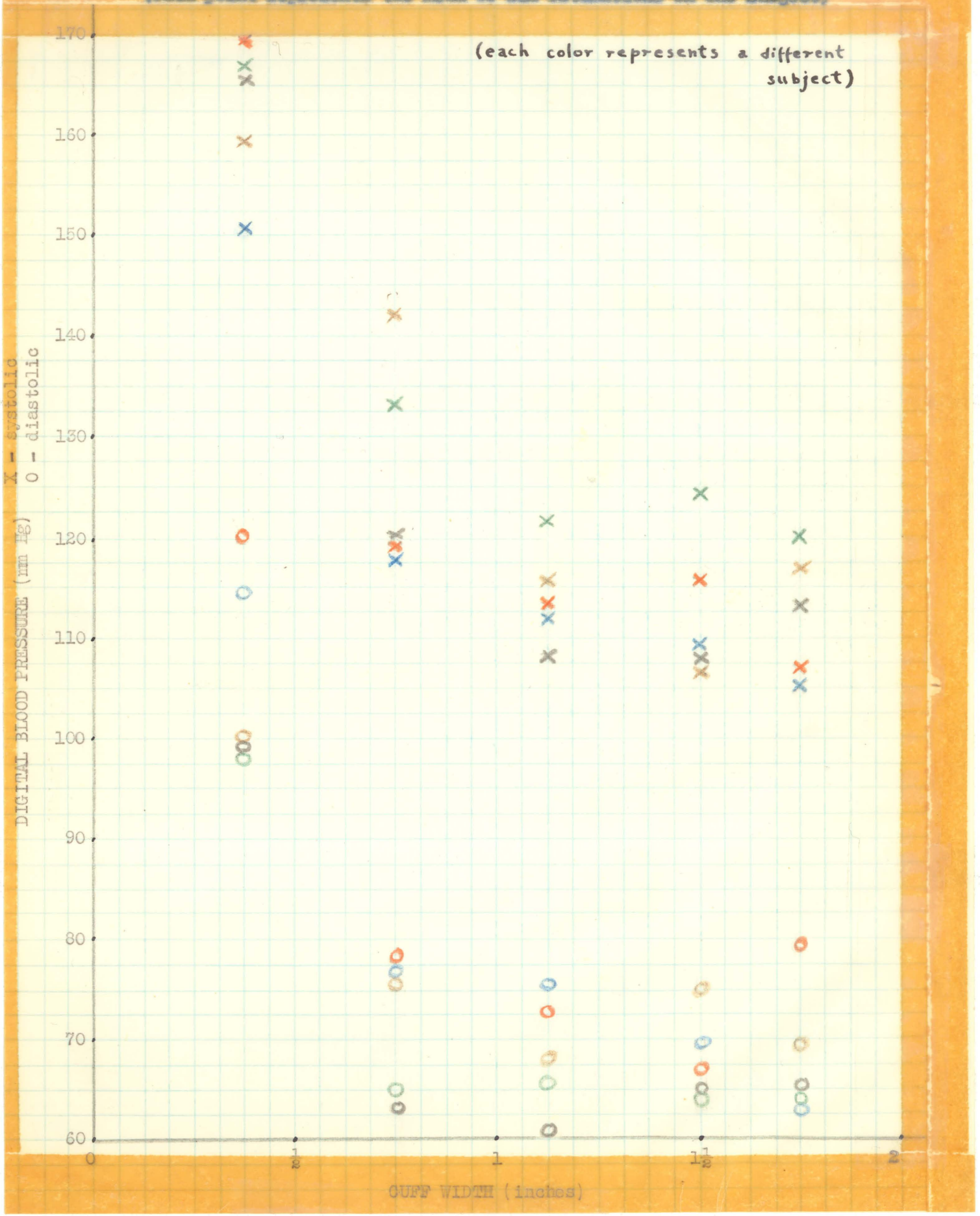


Table 2. A Comparison of Digital Systolic Pressures Measured by the Auscultatory and Visual Methods

Subject				Digital Systolic Pressure (mm Hg)		
				Auscultatory	Visual	Difference
S.C.	27 yrs	normal	male	109	104	+ 5
A.K.	25 yrs	"	"	112	112	0
A.G.	22 yrs	"	"	94	97	- 3
E.S.	22 yrs	"	"	95	97	- 2
L.O.	27 yrs	"	"	110	111	- 1
B.Z.	26 yrs	"	"	102	106	- 4
Mean				103.0	102.8	+ 0.3
				SE 4.4	SE 5.8	SE 1.5

Note: Each digital systolic pressure listed represents the mean of six estimations on one subject.

and was connected to a pressure reservoir with a manometer and to another tambour and mirror which reflected a light beam onto the same photosensitive paper. (see figure 4.) The finger cuff was inflated rapidly to well above systolic pressure. The cuff pressure was then gradually released. A signal light directed at the photosensitive paper was blacked out once each time the descending cuff pressure reached a 10 mm Hg marker on the manometer and several times in rapid succession when the systolic blood pressure was heard. The procedure was carried out three or four times on each of four normal males, age 20-28 years. Two of the subjects were kept very cool for thirty minutes before and all during the experiment, the other two were kept at a comfortable temperature. In all cases the auscultatory digital systolic pressure was within 3 mm Hg of the plethysmographic digital systolic pressure (i.e. the point on the plethysmographic tracing where the finger volume suddenly began to increase). (See figure 5.)

Because the digital systolic pressures measured by the auscultatory method were the same as those measured by the visual and plethysmographic methods, the auscultatory method has been accepted as reliable.

We believe that it is an improvement to use digital systolic pressure rather than brachial systolic pressure to represent the intravascular pressure of the finger. Yamada (102) claims that the brachio-digital systolic pressure difference never exceeds 3% and feels that any error introduced by using brachial systolic pressure is therefore negligible. Three experiments were carried out investigating the validity of Yamada's contention.

Experiment (a) The brachial systolic pressure and digital systolic pressure were both measured (alternately) six times in each of five normal males, age 22-27 years, who were allowed to remain at a

Figure 4. Apparatus for Comparison of Digital Systolic Pressures Measured by the Auscultatory and Plethysmographic Methods

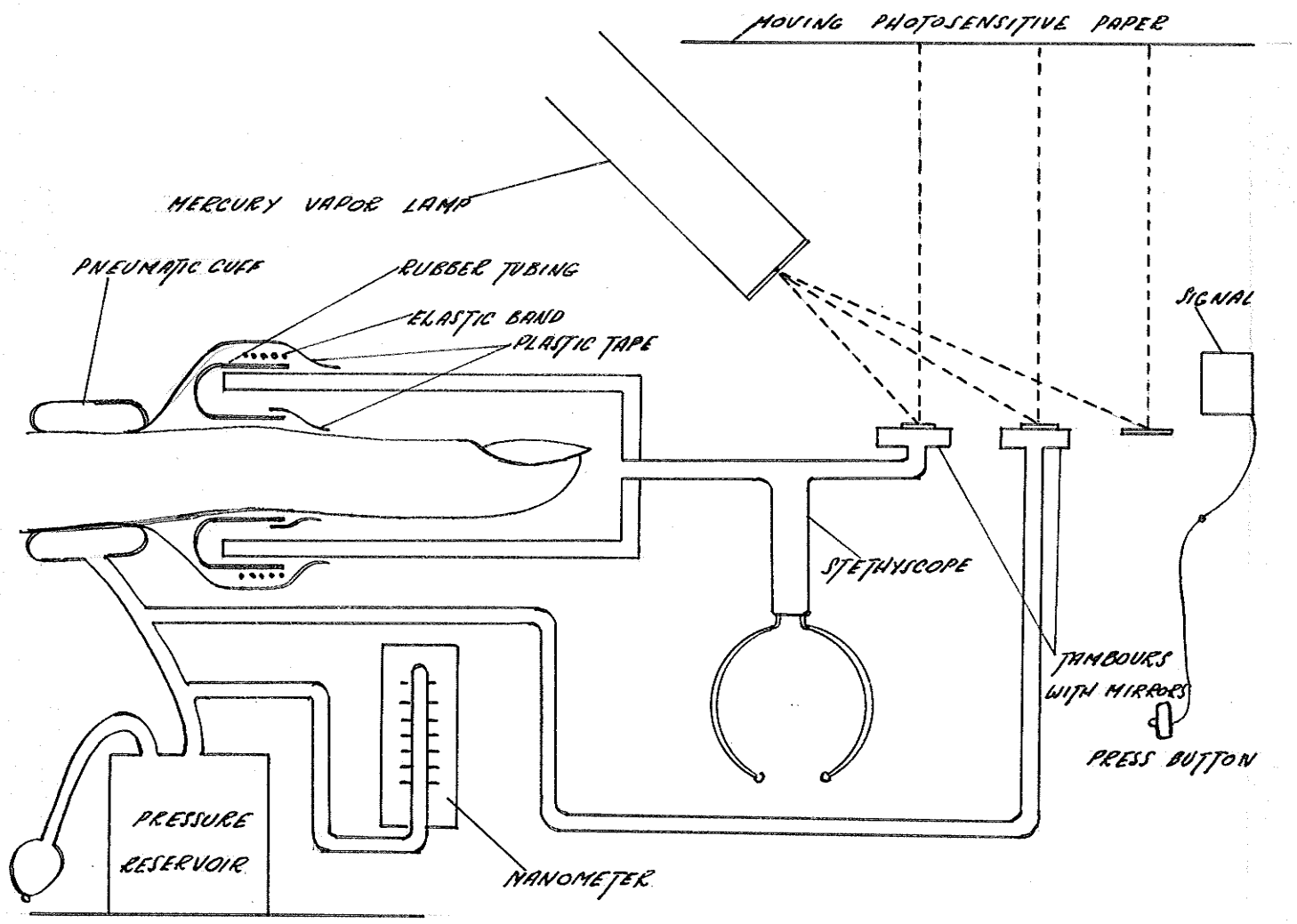
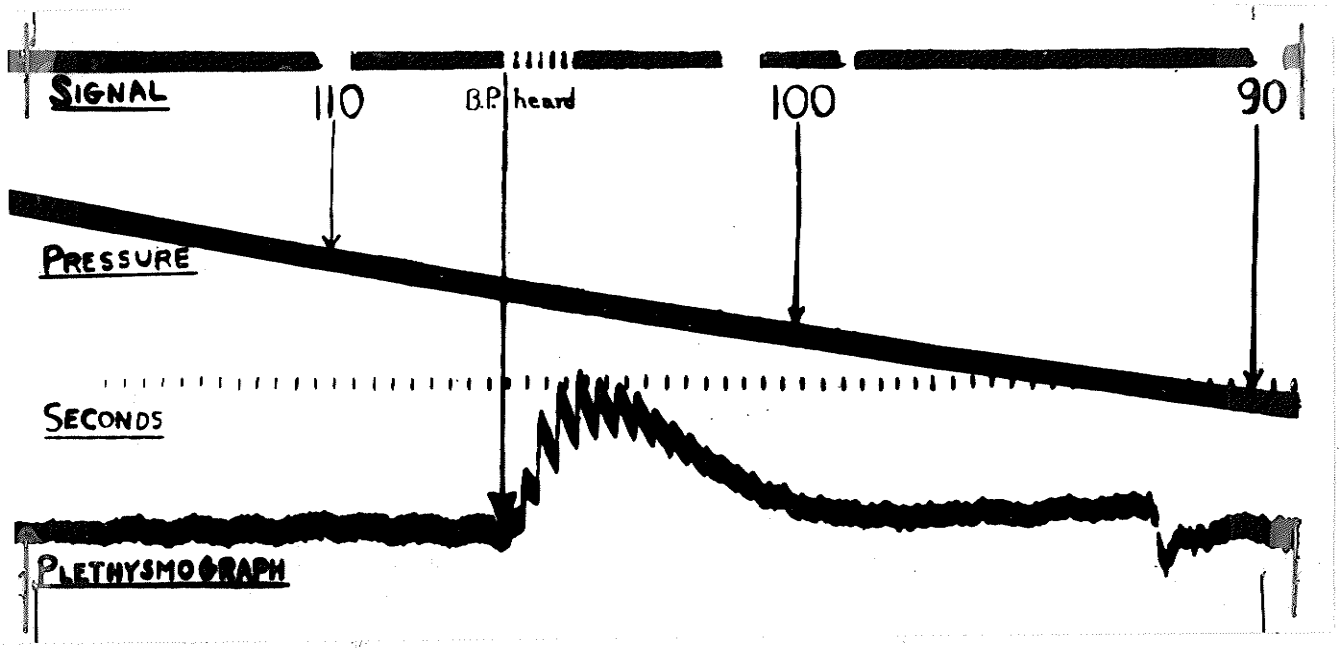


Figure 5. A Comparison of Digital Systolic Pressures Measured by the Auscultatory and Plethysmographic Methods



Note: This tracing is representative of those resulting from fourteen experiments on four different subjects.

comfortable temperature. In these subjects the brachio-digital systolic pressure gradient varied from 1-12% of brachial systolic pressure. (see table 3.)

Experiment (b) The brachial systolic pressure and digital systolic pressure were measured alternately in each of five normal males, age 22-27 years, six times when the subject was kept uncomfortably warm (vasodilated) and six times when he was kept uncomfortably cool (vasoconstricted). The brachio-digital systolic pressure gradient was found to be much greater when the subject was warm than when he was cool. (see table 4.) This is consistent with the findings of Doupe et al (27a) who measured digital systolic pressure by the plethysmographic method.

Experiment (c) The digital systolic pressure and brachial systolic pressure were measured alternately in six male and five female hypertensives, age 39-65 years, and three male and three female normotensives, age 37-54 years. Six estimations of both brachial systolic pressure and digital systolic pressure were taken on each subject while he was kept uncomfortably warm (vasodilated) and another six while he was kept uncomfortably cool (vasoconstricted). The brachio-digital systolic pressure gradient was found to be greater in hypertensives than in normotensives at both temperature extremes. As in normotensives, the gradient in hypertensives was greater when the subject was warm than when he was cool (see table 5.).

The procedures for regulated heating and cooling of subjects will be described in a later section.

The magnitude of the brachio-digital systolic pressure gradient and its variation with vasomotor state and blood pressure level would indicate that the errors introduced by using brachial systolic pressure to represent intravascular pressure when determining digital c.c.p. would be quite appreciable. (vs. Yamada).

3. Application of Extravascular Pressure:

An extravascular pressure, considerably greater than that required

Table 3. The Brachio-Digital Systolic Pressure Gradient in Normal Subjects at Comfortable Temperature

Subject				Brachial Systolic Pressure (mm Hg)	Digital Systolic Pressure (mm Hg)	Difference (mm Hg)
S.C.	27 yrs	normal	male	107	104	3 (3%)
A.J.	22 yrs	"	"	92	87	5 (6%)
H.S.	23 yrs	"	"	110	97	13 (12%)
I.S.	27 yrs	"	"	121	111	10 (9%)
D.Y.	26 yrs	"	"	107	106	1 (1%)
Mean				107.4	101.2	6.4 (6%)

Note: Each systolic pressure listed represents the mean of six estimations on one subject.

Table 4. The Brachio-Digital Systolic Pressure Gradient in Normal Subjects with Body Heating and Body Cooling

Subject				With Body Heating			With Body Cooling		
				B.H.P. (mm Hg)	D.H.P. (mm Hg)	Difference	B.H.P. (mm Hg)	D.H.P. (mm Hg)	Difference
S.G.	27 yrs	normal	male	128	94	34	127	119	8
A.G.	22 yrs	"	"	112	88	24	116	114	2
M.S.	22 yrs	"	"	120	102	18	121	113	8
I.S.	37 yrs	"	"	129	86	43	110	107	3
D.Y.	26 yrs	"	"	118	94	24	128	116	12
MEAN				121.4	92.8	28.6 ± 4.5	120.4	113.8	6.6 ± 1.8

Note: Each systolic pressure listed represents the mean of six estimations on one subject.

Table 5. The Brachio-Digital Systolic Pressure Gradient in Hypertensive and Normotensive Subjects with Body Cooling and Body Heating

Note: Each systolic pressure listed represents the mean of six estimations on one subject.

Subject.	With Body Cooling.			With Body Heating.		
	B.S.P. (mm Hg)	D.S.P. (mm Hg)	Difference	B.S.P. (mm Hg)	D.S.P. (mm Hg)	Difference
Hypertensives.						
H.B. 44 yrs male	200	198	2	202	195	7
A.L. 51 yrs female	221	203	18	216	181	35
H.B. 41 yrs "	227	207	20	207	158	49
S.B. 62 yrs "	240	214	26	232	203	29
E.D. 45 yrs male	166	156	10	167	140	27
E.L. 47 yrs "	166	148	18	160	137	23
C.C. 65 yrs female	215	197	18	200	149	51
E.F. 55 yrs "	218	198	20	217	181	36
J.L. 39 yrs male	200	192	8	198	168	30
R.J. 50 yrs "	140	131	9	124	101	23
J.S. 40 yrs "	232	197	35	199	168	31
MEAN 49.7 yrs.	200.4	185.5	14.9 Sx 3.1	192.1	160.1	31.0 Sx 3.7
Normotensives						
S.U. 47 yrs male	110	105	5	106	92	14
J.H. 33 yrs male	114	111	3	112	90	22
E.T. 37 yrs female	123	116	7	123	104	19
H.F. 51 yrs "	117	113	4	105	84	21
J.H. 44 yrs "	107	103	4	102	86	16
E.H. 54 yrs male	124	120	4	122	103	19
MEAN 45.2 yrs.	115.9	111.3	4.5 Sx 0.1	111.7	93.2	18.5 Sx 1.1

to stop flow, was introduced quickly into the plethysmograph from a pressure reservoir to which a manometer was connected. The eponychial capillaries were observed through the dissecting microscope. When flow in these vessels had ceased (within three minutes in most instances), the extravascular pressure was gradually released. That extravascular pressure at which flow resumed was noted.

4. Calculation of C.C.P.:

Immediately after the lowest extravascular pressure required to stop flow had been determined, the digital blood pressure was measured. The difference between the digital systolic pressure (intravascular pressure) and the lowest extravascular pressure required to prevent flow was taken as the C.C.P.

We feel that the direct method of noting blood flow through the finger holds an advantage over venous occlusion plethysmography in that it allows a temporally more accurate comparison of intravascular and extravascular pressures at the time of resumption of blood flow.

5. Precautions:

The following precautions have been taken in all of our experiments:

(a) The subject rested in the supine position for at least thirty minutes before and all during the experiment. In this way an attempt was made to stabilize his blood pressure and vasomotor state.

(b) The arm and hand were placed in such a position that the brachial and digital arteries were at approximately the same level. This was done in order to eliminate the effect of hydrostatic pressure in evaluating the brachio-digital gradient.

(c) The subject (unless designated otherwise) was kept at a comfortable temperature by being covered adequately in a room with a temperature of 68-72 degrees F. The procedures for heating and cooling a subject will be described later.

C. RESULTS

1. Preliminary Results of c.c.p. Measurement:

Taking the above precautions, the c.c.p. was measured in eight normal males, age 20-30. It was noted to be 9-40 mm. Hg (mean 25.0) (see table 6). These values are low when compared to those reported by Yamada (101). He found that the c.c.p. in five normal males at comfortable temperature ranged from 30-36 mm. Hg (mean 33.2). This discrepancy might be explained in part by the fact that Yamada used brachial systolic pressure rather than digital systolic pressure to represent the intravascular pressure and therefore his values for c.c.p. are increased by an amount equal to the brachio-digital systolic pressure gradient.

2. The Effects of Body Heating and Body Cooling on the c.c.p.:

The subject was heated with a warm water bath (into which his contralateral forearm was immersed) and an electric blanket until he was uncomfortably warm and perspiring. With the subject in this state the c.c.p. was measured. He was then cooled by having the blanket and most of his clothing removed and his contralateral arm immersed in cold water until he was uncomfortably chilly and shivering. With the subject in this state the c.c.p. was again measured. Three normal males, age 23-27 years were tested in this fashion. Another three normal males, age 25-26 years, were tested in the same way except that they were cooled before they were heated. In all six subjects the c.c.p. was found to be higher when the body was cooled than when the body was heated (see table 7).

A more accurate regulation of body temperature seemed unnecessary in this qualitative experiment in which each subject served as his own control.

3. The Effect of Conduction Anaesthesia on the c.c.p.:

The c.c.p. was measured in the ring and index fingers of the same hand. Following this a digital nerve block on one of the two fingers was effected with two cc. of 1% procaine. The control finger was injected with

Table 6. The C.S.F. in Normal Subjects at Comfortable Temperatures

Subject				C.S.F. (mm Hg)	Intravenous Pressure Required to Stop Flow (mm Hg)	C.S.F. (mm Hg)
S.C.	20 yrs	normal	male	114	205	9
J.W.	20 yrs	"	"	95	60	35
S.C.	27 yrs	"	"	104	80	24
A.K.	25 yrs	"	"	112	102	10
A.G.	32 yrs	"	"	87	56	31
M.S.	22 yrs	"	"	97	82	15
I.S.	27 yrs	"	"	111	91	20
B.Y.	26 yrs	"	"	106	66	40
MEAN						22.0 ± 4.2

Note: Each reading listed represents the mean of six estimations on one subject.

Table 7. The C.C.F. in Normal Subjects with Body Heating and Body Cooling

Subject				C.C.F. With Body Cooling (mm Hg)	C.C.F. With Body Heating (mm Hg)	Difference (mm Hg)
K.F.	26 yrs	normal	male	42	18	24
L.F.	26 yrs	"	"	31	9	22
A.K.	25 yrs	"	"	34	28	6
J.R.	23 yrs	"	"	49	5	44
D.X.	26 yrs	"	"	51	7	44
K.M.	25 yrs	"	"	34	12	22
MEAN				40.2 Sx 3.4	13.2 Sx 2.5	27.0 Sx 6.9

Note: Each c.c.p. listed represents the mean of six estimations on one subject.

two cc's. of normal saline. The c.c.p. was again measured in the two fingers. This experiment was carried out on three normal 26 year old males. In each case the c.c.p. was significantly decreased following procaine injection and statistically unchanged after saline injection (see table 8).

4. The Effect of Local Ischemia on the c.c.p.:

Experiment (a): A suprasystolic extravascular (intraplethysmographic) pressure was maintained for a period of time ranging from 45 seconds to 11 minutes. This pressure was then released gradually until synovial flow resumed. The c.c.p. measurement was completed in the usual way. A rest period of a duration at least equal to the time of ischemia was allowed before reapplication of the extravascular pressure. The c.c.p.'s thus measured were plotted on a graph against the duration of local ischemia. (see figure 6). The graph suggests that local ischemia has a diminishing effect upon the c.c.p. This diminishing effect seems to increase with the duration of the local ischemia until that duration has reached about two or three minutes. Further ischemia seems to have no added effect.

This experiment, however, was carried out only once (on a 39 year old normal male). Further attempts at the same experiment proved unsuccessful because the suprasystolic extravascular pressure did not stop synovial flow until about two minutes had elapsed and therefore it was impossible to determine the c.c.p. after a period of ischemia of less than two minutes.

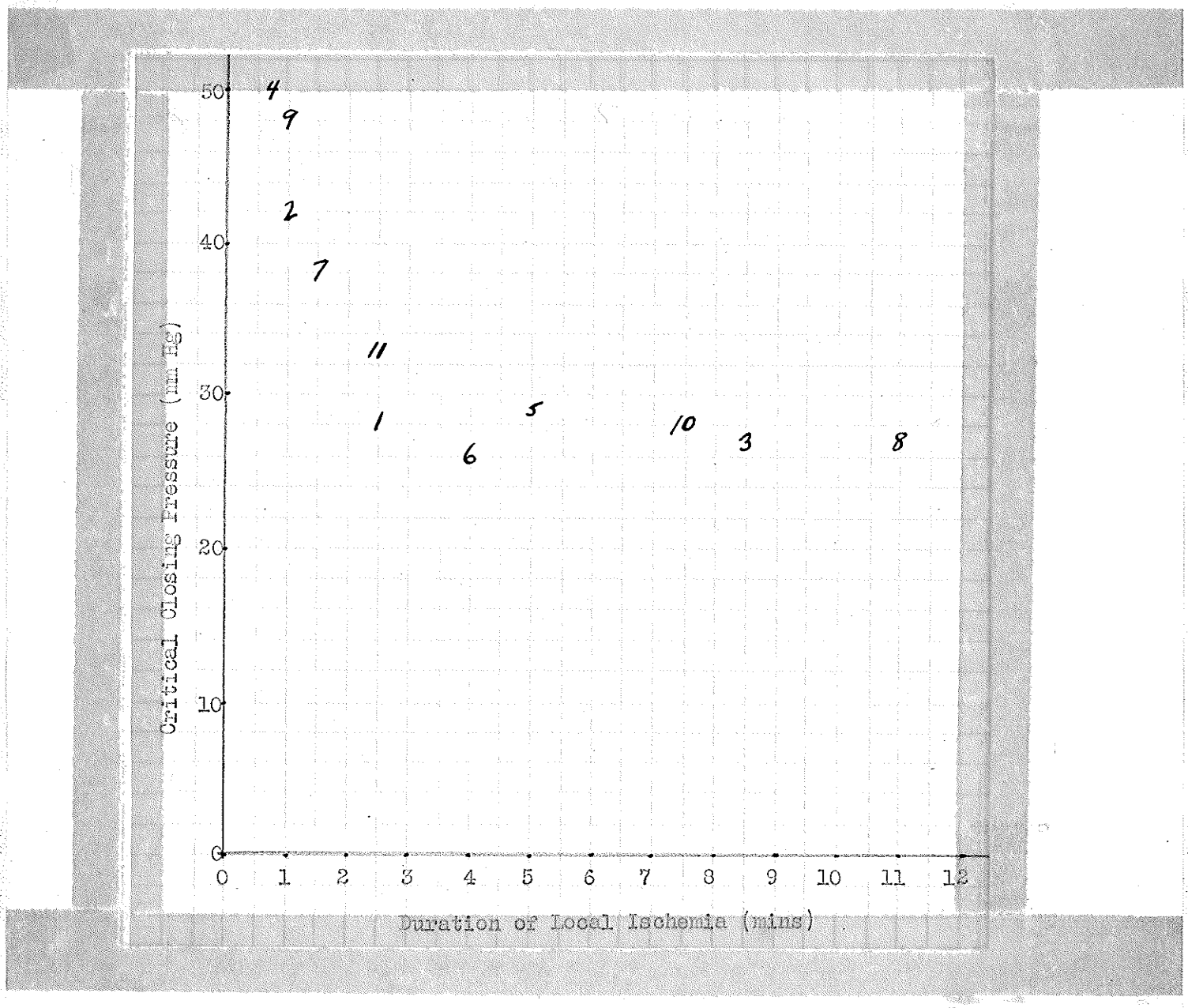
Experiment (b): Suprasystolic extravascular pressure was maintained for three minutes and then c.c.p. was measured. Following a three minute rest period, suprasystolic extravascular pressure was maintained for ten minutes and c.c.p. was again measured. After ten minutes of rest the procedure was repeated. The experiment was continued until twelve c.c.p.'s had been measured, six after three minutes of local ischemia, and six after ten minutes of local ischemia. Two normal males and two normal females, age 28-39 years were tested. In all cases the c.c.p. was found to be

Table 6. The Effect upon the C.C.P. of Conduction Anaesthesia of the Finger

		C.C.P. Before Ischaemia (mm Hg)	C.C.P. After Ischaemia (mm Hg)	Difference (mm Hg)	C.C.P. Before Exercise (mm Hg)	C.C.P. After Exercise (mm Hg)	Difference (mm Hg)
N.P.	26 yrs normal male	21	19	2	25	15	10
L.P.	26 yrs " "	26	26	0	28	12	16
D.Z.	26 yrs " "	29	33	-3	31	16	15
MEAN				-0.3 S.E. 1.4			13.0 S.E. 1.7

Note: Each C.C.P. listed represents the mean of six estimations on one subject.

Figure 6. The Effect of Local Ischemia upon the C.C.P.



Note: This graph is representative of the results of only one experiment.
The plotted numbers indicate the sequence in which the eleven readings were taken.

statistically the same after three minutes of local ischemia as after ten minutes of local ischemia (see table 9).

In all c.c.p. experiments three to ten minutes of local ischemia preceded c.c.p. measurement. In this way any effect of local ischemia on the c.c.p. was standardized.

5. The Effect of Increased Venous Pressure on the c.c.p.:

A brachial cuff was inflated with a pressure slightly below digital systolic pressure and was kept on the arm until the venous pressure (as measured by a Sanborn manometer connected to a vein on the dorsum of the hand by a 20-gauge needle) reached a level well above the original digital diastolic pressure. With the brachial cuff still applied, the c.c.p. was measured. The brachial cuff was then released and c.c.p. was again measured immediately. A ten minute rest period then was allowed. The procedure was repeated four times on each of four normal males, age 22-27 years. It was found that the c.c.p. at normal venous pressure and at greatly elevated venous pressure was statistically the same (see table 10).

6. The c.c.p. in Hypertension:

Yamada (103) measured the c.c.p. in 17 essential hypertensives at comfortable temperature and found that it ranged from 68-170 mm. Hg (mean 118.4). As mentioned previously, the values that he reported for five normals at comfortable temperature were 39-66 mm. Hg (mean 56.2).

Because c.c.p. seems to vary with the degree of vasodilatation or vasoconstriction, an attempt was made in the following experiment to control the vasomotor state by standardizing the local skin temperatures at which c.c.p.'s were measured.

The test finger was prepared in the usual way for c.c.p. measurement. Thermocouples for skin temperature measurement were attached to the finger on each side of the test finger. The mean of the two temperatures recorded by the thermocouples at a given time was taken as the skin

Table 9. The C.C.P. after 3 Minutes and after 10 Minutes of Local Ischemia

Subject				(mm Hg) C.C.P. 3 mins	(mm Hg) C.C.P. 10 mins	Difference (mm Hg)
E.T.	37 yrs	normal	female	28	30	-2
F.G.	39 yrs	"	male	26	27	-1
A.G.	22 yrs	"	"	20	19	1
V.Y.	24 yrs	"	female	26	25	1
MEAN						-0.25 S.E. 0.7

Note: Each c.c.p. listed represents the mean of six estimations on one subject.

Table 10. The Effect upon the C.C.P. of Elevating the Venous Pressure

	Brachial Cuff Applied					No Brachial Cuff (venous pressure 0-10)		
Subject	Brachial Cuff Pressure (mm Hg)	Venous Pressure (mm Hg)	Extra-vascular Pressure Required to stop Flow (mm Hg)	Digital Blood Pressure (mm Hg)	C.C.P. (mm Hg)	Extra-vascular Pressure Required to stop Flow (mm Hg)	Digital Blood Pressure (mm Hg)	C.C.P. (mm Hg)
G.W. 26 yrs.	105	96	72	110-97	38	74	114-78	40
normal male	100	90	70	106-90	36	73	112-80	39
	95	93	70	103-92	33	73	107-78	34
	92	91	64	101-90	37	74	109-76	35
S.C. 27 yrs.	94	92	85	104-92	19	81	102-66	21
normal male	96	94	80	103-96	23	83	106-70	23
	100	97	86	107-98	21	84	108-70	24
	93	94	82	106-93	24	84	106-68	22
P.P. 25 yrs.	95	85	66	99-84	33	68	100-62	32
normal male	100	94	68	100-95	32	68	102-66	34
	94	84	66	98-86	32	65	99-64	34
	90	83	68	100-82	32	65	98-62	33
A.G. 22 yrs.	97	93	76	104-92	28	76	103-66	27
normal male	96	90	75	98-90	23	78	101-63	23
	92	89	73	96-88	23	77	100-64	23
	90	85	74	99-86	25	75	102-65	27
MEAN					28.7 Sx 1.5			29.4 Sx 1.6

Note: All readings listed above represent the result of only one estimation.

temperature of the fingers. Room temperature was kept at 20-22 degrees C. By having the subject lie lightly covered with his contralateral arm immersed in a water bath (temp 16-19 degrees C.) he was cooled until his skin temperature was within two degrees C. of room temperature. With the subject in this state, c.c.p. was measured. Then by having the subject lie covered by an electric blanket with his contralateral arm immersed in a water bath (temp 44-45 degrees C.) he was heated until his skin temperature was two to four degrees C. less than his body temperature (37 degrees C.). With the subject in this state c.c.p. was again measured. The procedure was carried out on five male and five female hypertensives, age 39-65 years and three male and three female normotensives, age 58-64 years. The c.c.p. was found to range in the hypertensives from 44-68 mm. Hg (mean 52.0) when cold and from 13-23 mm. Hg (mean 19.1) when hot and in normotensives from 23-36 mm. Hg (mean 27.7) when cold and from 9-18 mm. Hg (mean 11.7) when hot. (see table 11). In other words in both a state of regulated vasoconstriction and a state of regulated vasodilatation the c.c.p. was significantly higher in hypertensives than in normotensives.

D. DISCUSSION

1. A Review of Factors That Might Be Considered Responsible for c.c.p. as Measured.

(a) Venous Pressure: Girling (35) considered the possibility that the c.c.p. might be really a measure of the venous pressure of the part. He went on to show however that in rabbits the c.c.p. greatly exceeded the measured venous pressure. We found in normal humans that at normal venous pressure the c.c.p. was greater than the venous pressure and that when the venous pressure was elevated by means of a brachial cuff to a level well above the c.c.p. (as measured at normal venous pressure) the c.c.p. remained statistically unchanged (see table 10). These findings seem to

Table 11. The C.C.P. in Hypertensive and Normal Subjects with Body Cooling and Body Heating

Subject	With body cooling: Room Temp (°C)	Skin Temp (°C)	Brachial Blood Pressure (mm Hg)	Digital Systolic Pressure (mm Hg)	Extra-vascular Pressure Required to Stop Flow (mm Hg)	C.C.P. (mm Hg)	With body heating: Skin Temp (°C)	Brachial Blood Pressure (mm Hg)	Digital Systolic Pressure (mm Hg)	Extra-vascular Pressure Required to stop Flow (mm Hg)	C.C.P. (mm Hg)
Hypertensives											
N.B. 44 yrs. male	20	21.4	220-124	198	147	51	33.7	202-122	195	175	20
A.L. 51 yrs. female	20.5	22.2	221-130	203	151	52	33.6	216-129	181	158	23
H.B. 41 yrs. female	20	21.0	227-122	207	139	68	33.6	207-121	138	136	22
S.B. 62 yrs. female	20	21.2	240-135	214	159	55	33.8	212-120	183	165	18
E.B. 45 yrs. male	22	23.9	166-112	156	112	44	33.9	167-116	140	121	19
E.L. 47 yrs. male	21	21.8	166-111	148	99	49	34.0	160-113	137	119	18
C.C. 65 yrs. female	21	22.8	215-107	197	153	44	34.7	200-100	149	132	17
M.F. 55 yrs. female	21	22.4	218-91	198	145	53	33.3	217-90	181	168	13
J.L. 39 yrs. male	21	22.7	200-115	192	140	52	33.9	198-113	168	146	22
J.S. 48 yrs. male	21.5	23.0	212-105	195	145	52	33.4	199-102	168	149	19
MEAN 49.7 yrs.						52.0 Sx2.1					19.1 Sx 0.3
Normotensives											
S.U. 47 yrs. male	21	22.6	11-74	105	82	23	33.3	106-71	92	81	11
J.H. 38 yrs. male	20	21.6	114-71	111	85	26	33.4	112-69	90	80	10
E.T. 37 yrs. female	21	22.9	123-83	116	87	29	35.0	123-78	104	95	9
F.H. 54 yrs. male	21.5	22.8	124-80	120	93	27	33.6	122-79	103	91	12
M.F. 51 yrs. female	22	23.8	117-83	113	77	36	33.4	105-67	84	66	18
J.M. 44 yrs. female	22	23.3	107-68	103	78	25	34.7	102-65	86	76	10
MEAN 45.2 yrs.						27.7 Sx 1.8					11.7 Sx 1.3

Note: Each reading listed represents the mean of six estimations on one subject.

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rule out the possibility that the c.c.p. is a measure of venous pressure.

(b) Tissue Pressure: Thus far it has been assumed that normally the tissue pressure is negligible. Girling (35) states that there cannot be any significant degree of tissue pressure without gross edema. Because no such edema was noted at any time during our experiments, we feel that tissue pressure was not responsible for an appreciable part of the measured c.c.p. Nichol et al (68) reported that in frogs the advent of gross edema was not accompanied by a significant change in the c.c.p.

(c) Viscosity: It has been pointed out earlier that since c.c.p. is measured when flow has just resumed, viscous resistance, which is proportional to rate of flow, must be negligible.

(d) Blockage of Vessels: We have not considered very seriously the possibility that blockage of vessels (presumably by the formed elements of the blood) accounts for c.c.p. because c.c.p. was measured originally by Nichol et al (68) using Ringer's Solution, a non-clotting fluid, as the perfusion fluid.

(e) Yield Pressure: Fulton (33) explains in his text that from a rheological standpoint there are two types of fluid: (i) viscous or Newtonian fluids the flow rate of which (through rigid tubes of uniform bore) is strictly proportional to the perfusion pressure and (ii) plastic fluids or Bingham bodies the flow rate of which becomes zero at a positive critical perfusion pressure, the yield pressure. The possibility arises that c.c.p. is really a measure of the yield pressure of the blood. The work of Whittaker and Winton (99) seems to support this possibility. They plotted pressure-flow curves through the hind leg of a dog using Ringer's solution (a viscous fluid) and blood (a plastic fluid) as perfusion fluids. With Ringer's solution their curves appeared to pass through the origin, while with blood their curves intersected the pressure axis at a positive value.

The slowest flow actually recorded by Whittaker and Winton with Ringer's solution, however, was 140 ml/minute at a perfusion pressure of 35 mm. Hg. Their curves reached the origin by means of a long extrapolation which seems hardly justified. Mahol et al (60) plotted pressure flow curves through the hind limb of a rabbit. They also used Ringer's solution and blood as perfusion fluids, and found that with both fluids their curves intersected the pressure axis at positive values, frequently similar. These investigators plotted actual flow-pressure relationships right down to the point where flow ceased. Their findings are accepted therefore as being more reliable than those of Whittaker and Winton. Copley et al (13), using a rolling ball viscometer, calculated the yield pressure for blood. His values are very small when compared with our c.c.p. values. It is concluded that the yield pressure of blood does not account for a significant part of the c.c.p. as measured.

(f) Intradigital Systolic Pressure Gradient: Digital blood pressure is measured at a point proximal to the point of critical closure. The question arises: Is c.c.p. actually a measure of the systolic pressure (intravascular pressure) gradient between these two points? Because the intravascular pressure at all points in the vascular loop (from artery to vein) must be equal to or greater than the venous pressure, the intradigital pressure gradient cannot exceed the difference between the digital systolic pressure and the venous pressure. When the venous pressure was elevated by means of a brachial cuff, the difference between digital systolic pressure and venous pressure ranged from 6-17 mm. Hg while the c.c.p. ranged from 19-38 mm. Hg (see table 10). The intradigital systolic pressure gradient, therefore, could not be totally responsible for the c.c.p. as measured.

(g) Vascular Tone: Burton (9) feels that c.c.p. is the product of vascular tone. Nichol et al (68) supported Burton in this regard by showing that drugs known to increase vascular tone cause an elevation of the c.c.p. in experimental animals. We found in humans that the c.c.p. was higher when the body was cooled than when the body was heated (see table 7), and that the c.c.p. was decreased by conduction anaesthesia (see table 8) and probably by the first two or three minutes of local ischemia (see figure 6). All of these findings are compatible with Burton's contention that c.c.p. is the product of vascular tone.

The c.c.p. was found to be higher in hypertensives than in normotensives (see table 11). If we accept the theory that c.c.p. is the product of vascular tone it follows that the vascular tone is increased in hypertension.

2. Suggestion for the Future Application of c.c.p. Measurement:

(a) Diagnosis: In essential hypertension and toxemia of pregnancy increased vascular tone is believed to be the basic abnormality. In such conditions one would therefore expect to find an increased c.c.p. The degree of depression of this elevated c.c.p. that would be effected by a conduction anaesthesia of the test finger might yield considerable information as to the origin of the increased vascular tone (i.e. neurogenic or non-neurogenic). Such information might be of value in selecting therapeutic measures.

(b) Evaluation of Therapy: In conditions characterized by an increased vascular tone, the success or failure of various therapeutic measures might be assessed on the basis of their ability to lower the c.c.p.

E. CONCLUSIONS:

(1) A method for measuring c.c.p. (as defined by Burton) in the human

finger has been developed.

(2) In eight normal males kept comfortable in a room temperature of 68-72 degrees F. the c.c.p. ranged from 9-35 mm. Hg (mean 23.0).

(3) The c.c.p. is higher when the body is cooled than when the body is heated.

(4) The c.c.p. is decreased by conduction anesthesia.

(5) The c.c.p. was decreased during the first two or three minutes of local ischemia in the one subject in whom c.c.p. could be measured after less than two minutes of local ischemia. There is no difference between the c.c.p.'s measured after three minutes of local ischemia and those measured after ten minutes of local ischemia.

(6) The c.c.p. is the same at supradiastolic venous pressure as it is at normal venous pressure.

(7) The c.c.p. is higher in hypertensives than in normotensives in both the vasoconstricted and vasodilated states.

(8) The hypertension in toxemia of pregnancy is probably the result of increased vascular tone. Since c.c.p. is believed to be an index of vascular tone, it is suggested that c.c.p. measurement might be of value in determining the nature of toxemic hypertension and assessing therapeutic measures aimed at correcting it.

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